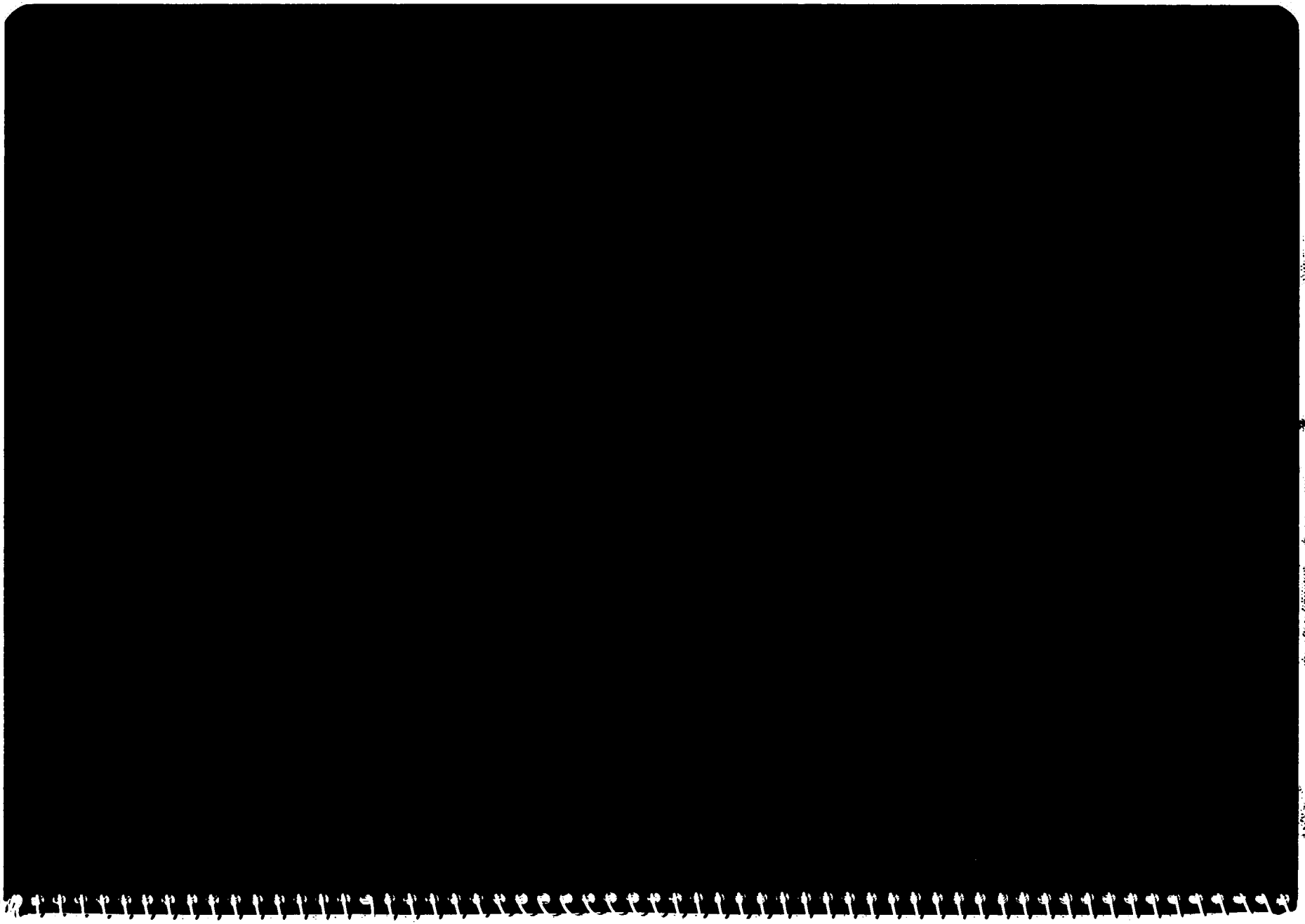

Tuesday March 16th 1993:-

Cuttings from ACJ. # 5870 → # 5888.

#5870 - "Smokers' sperm spell trouble for future generations"
Could there be any comparison between this and the radiation
studies. Either through the Gardener report on radiation
at Sellafield or Mururoa Radiation report re record generation
chromosome abnormalities.
Bruce Ames calls for more antioxidants in diet to overcome
this. - N.B try trace amoles

Bunny may catch....

From lit search from Rosemary on atherosclerosis and smoking in animals...

Ref #6:
Penney, D.G. & Hadley, J.W. (1991)
"Is there a connection between carbon monoxide exposure and hypertension"
Environ Health. Perspect. 1991 Nov. 93: p91-8.
States:-
"It has been asserted that chronic CO exposure increases the development of atherosclerotic disease; however, convincing evidence from animal experimentation is lacking". Nevertheless, CO may elevate plasma cholesterol and does appear to enhance atherosclerosis when serum cholesterol is greatly elevated by diet".

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Info:- Questions for info -

① Thesis re melanin incorporation of nicotine - can we have a copy?

② Blood nicotine & urine nicotine from systemic uptake in SD & BN.

③ Washing effects - what to look for

④ What is involved in getting enough experimental data for publication of animal data - objective being to show negligible effect of rat/human systemic uptake in rats

Our future objectives:- Main aim to identify possible confounders (& how they work?)
How treatment factors -
Quantitation of human systemic uptake not high priority - probably not even very necessary
Mechanisms of loading - highly relevant to explain washing effects etc - but not necessary to put too much weight on it.

Chief objective = to establish publication of animal data
- to establish the 'spurious' effects noticed & how strong are their foundations

---

To pass on - information from PSIs overheads/calculations.

① Raw data (Table 3) from Nilsen not possible - just ate at Nilsens data -

② overhead to activate systemic uptake

③ NC data - not to be used in publication but o.k. for predictions only.
Low absorbers & high absorbers

④ Slopes for the 80 subjects.

⑤ errors likely on systemic - cannot justify much more work on systemic

- Rang Wolf - O.K. - not much significant new data but some ends to tidy up
re Teredesai paper & Vaccher paper - comments from Jon -
Wolf will ring me back at around 3.00

re Jones - nothing that Wolf knows of - some evidence of convulsive movement but not specific enough etc etc.

Wednesday March 24th.

Phone call from RCA -

1) Bunny study ... O.K. - in Lofo protocol - to be discussed further with Ragnar Rylander in April.

2) E.P.A spokespersons - RDE, RIT & HEE - : will require media training - check that we have E.P.A. documentation.

To do - Write / Profs to WRE re R&D seminars - preferable dates Wed Oct 27th ~~and~~ or Feb 23rd.

- See Ted - re Lofo testing potential - R&D projects.
- Send H-AB abstract to Dr Baumann
- Send ISEC write-up and programme for Brussels to WRE
- Ask Richard re NIH strategy plan for 21st century - will we get a copy? - what happened / happening re priorities.
- Ring Nine No / Kuan regarding trip from Helsinki to Switzerland in June - any suggestions re ferries etc ... - Copenhagen?
- passaring to Mayoda
- See MMH about R&D seminars
- Finish Spanish presentation
- Write up notes / plan from Lofo visit.

Current Contents: - Feb 15th 1993 36#7

Multidisciplin -	24-35	~~181-211~~
Biochem & Biophys -	52-88	~~211-194~~
Mol Biol & Genetics -	88-103	~~264-2~~ ✓
Microbiol & Cell Biol.	103-118	~~273-1~~
Pharmacology	118-141	~~274-113~~
Immunology	141-149	259 338
Expal Biol & Med	155-200	
Clinical Med.	200-253	
Neurosciences & Beh.	253-282	

2028541586

Thursday March 25th 1993

- Phone call to Mitch.
- Phone Tony Andrade re bunny study.

EACR Meeting - Brussels Apr 5-7 -

Parallel Symposia:-

Monday 5th - 3.30 → 5.45 = LR,B
- №1 Mol Aspects of Diagn of Cancer
- №2 New trends in Cancer Chemoth ?
- №3 Viruses & Cancer.

Tuesday 6th - 9.45 → 12.00 =
- №4 Molecular epidemiol of Cancer ? *
- №5 Cell cycle regulation & Cancer
- №6 Antibodies in Cancer treatment

Wednesday 7th - 3.00 → 5.15 =
- №7 Tumour suppressor genes
- №8 Environmental carcin: Exp & Meds. *
- №9 Mechs of Drug Resistance.

Wednesday 7th - 9.45 → 12.00 =
- №10 Growth Factors *
- №11 Mol. Aspects of Invasion & Metastasis
- №12 Cell responses against cancerous

3.00 → 5.15 =
- №13 Ovarian Cancer: Mol. & Clin Aspects ?
- 14 Oncogenes
- 15 Gene therapy in Cancer.

Rung Bob - Thanks for article on "Molecular Toxicology"
*Remark: EPA spokesperson - what will it mean?

#

F.X. Adlkofer, 1993. Zbl. Arbeitsmed. 42 (1992) 100-104.

"Lung Cancer through passive smoking at the workplace - a more theoretical issue"
(Original article in German - English summary as below ...)

ETS differs in composition and biological activity from mainstream smoke inhaled by the smoker to such an extent, that the amounts of toxic substances taken up by exposure to ETS cannot be expressed in terms of cigarette equivalents. In contrast to smoking, the uptake of gaseous phase constituents is of major importance during exposure to ETS whereas the uptake of particle phase constituents, to which the development of lung cancer has been attributed, is very low. Moreover, ETS is inevitably mixed with substances from other sources. *

Under experimental conditions, inhaling exposure to ETS 30x higher conc of tobacco smoke than found under normal conditions, non smokers

show slightly elevated levels of COHb in blood and nicotine and cotinine in body fluids as well as an elevated ~~level~~ excretion of benzene in exhalate and of tricloromethane in urine. The two last mentioned provide evidence for the uptake of electrophilic, i.e. potentially carcinogenic, substances from the gaseous phase. In contrast to smokers, neither an increase in DNA-adducts in monocytes nor an elevation in urinary mutagenicity could be found in non-smokers despite an extreme exposure to ETS. In non-smokers exposed to ETS at the workplace, only nicotine or its metabolite cotinine are likely to be found in body fluids. All other parameters, particularly those indicating genotoxic effects are indistinguishable from the background levels.

The results from 30 epidemiological studies on exposure to ETS are currently available. Most of these studies show a relative risk of >1 (mean value: 1.35), but a significant increase in risk is found in only a few cases, and it has rarely been possible to demonstrate a dose-response relationship. Any elevated risk is most probably "due to methodological errors of which misclassifying smokers as non-smokers and disregarding confounding factors are the most significant. The present analysis leads us to conclude that a lung cancer risk due to ETS can neither be entirely ruled out nor proved, let alone quantified. If the risk really exists, it must be extremely low. Therefore, if ETS does not constitute a major lung cancer risk, the working population would not benefit from confining the reduction of toxic substances to tobacco smoke ~~beings~~ by bans on smoking as toxic substances from other sources present at the workplace might be ignored by this procedure."

? for HER. – Is this true – re gaseous v particulate uptake of ETS? *

N.B.:- C.R.E. Coggins et al. 1993. Inhalation Toxicology, 5:77-96.
"Subchronic inhalation study in Rats using aged and diluted SS smoke from a reference cigarette".

- Doses used = 0.1*, 1 & 10 mg of particle / M^3.
Only effect = slight to mild epithelial hyperplasia in nasal nasal cavity in 10 mg group only.
Based on this NOEL for 90 day study estimated at > 1 mg/M^3 *

? for HER - what are "acceptable" ETS particulate conc's. *

Tomorrow:-

- Pull together package on burning study, for Tony Andrade including my printed & 'ejected' parts' - & begin planning where info & I thought we should be going.....

- Communicate to info re R&D Seminars; ISREC write-up; GACR conference.

* HER - info to date to visit 21st/22nd. *

Spain Conference:- HBI international conference 3 Spanish cities
* Mid April - beginning of May:- * 13, 15, 17th May.

* WRE 21st / 22nd. *

Monday 29th May*

~~① finish Prof note to WRE regarding R&D seminars~~
~~② Rung Lee/Lee re notice to Uni for meeting next week~~
*③ Prof note to Spanish people re possibility of presentation *
*④ Finish Spanish presentation *
~~⑤ Prepare for talk w Tim re info~~
*⑥ Order TIBS: October 1992. Signal transduction issue *

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Inbifo:

① Product testing after development

② Identification of mechanisms of action w potential to indicate direction for product design.

③ Identification of biological activity (smoking & health aspects)

[④ Method development in prepn of ①, ② or ③ above)

① = ~~No comment~~ need feedback from P.dev. to know what ⇒

② "Intensity"
Odour / staleness etc. } ④ Method dept

③ bunny study - possibly leading to mechs.

④ Id of tests to identify poss biol effects of ETS?

Signal transduction :- ~~43 — 845~~

Ep. ~~18?~~ 203
~~197~~ 24, 45, 65
~~206 — 239~~
~~266 — 57~~

~~109 — 65~~
~~234 — 91~~
~~239 — 84, 184, 33, ...~~
~~240 — 3, 63, 73, 7, ...~~

~~159 — 418~~
~~260 — 1655~~
~~263 — 149, 166~~
~~254 — 29, 37, 318 ...~~
~~264 — 173, 180, 313~~
~~269 — 65~~
~~131 — 31~~
~~257 — 521~~
266 — 75

* 4-AS. * ⇒ ESA

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March 30th Dr Hamman: R&D Seminar - decision will be made when Wolf comes back in 3 weeks

re Brukelles - very general - nothing specific they are interested in - but would like to know after.....

Dr Walk. 00 32 2 720 51 74.

[Tuesday 6th :- Dinner Host - 19h] Hotel Metropole

Take financial procedures documentation up to him.

- Ask Roger to send/bring details of references on the 'biochemical' methods he talked about before:-

* ETS Network development group - Wed Apr 11th: NCNDs, CNRS, D.Mag..... can Pou/Hee attend..... *.

Literature:-

"K-ras Mutations in Human adenocarcinoma of the lung: association with smoking and occupational exposure"

K. Husgafvel-Pursiainen et al (Helsinki, IARC) Int. J. Canc. 53: 250-256 1993.

Lobectomy or pneumonectomy lung cancer patients bet 1988-1991

= 45 patients out of 122 ~~had~~ suspected had tumour.

No chemo or radiotherapy.

Fresh tumour & peripheral lung samples taken

DNA from white blood cells, homogenised tumour tissue & peripheral lung tissues.

PCR amplification of codons 12, 13 & 61 K-ras, N-ras
12 & 61 only H-ras

Probed with synthetic ON probes & Dot blot hybridisation

Results: No mutation identified in N-ras or H-ras

In K-ras = 14/45 mutations (29%)

12/21 mutations in adenocarcinoma

10 Transversions, 4 Transitions

G→T = 8/14. 7 = G→A at first base of codon 12, or 13 etc etc.....

No mutation in normal tissue (other than explicable cases)

Comparison of Table III with Table I.

Under the assumption that all the mutation found are shown in Table 3- could make a comparison of three groups regarding Aspects exposure, eg smoking, & age etc etc.... These 3 groups being:-

	Pack years:-	AD Exp. $f \times 10^6/g$
Patients showing mutation (14)	52.6	4.4 (top exp. ind.) 2.7 = 4
Patients not showing mutation (34)	38	4.9. (- top exp. ind.) 1.39
Total population (all 48)	= 45	557

Shuzyi Kato et al (1992)

Cytochrome P450 IIE1 Genetic Polymorphisms, Racial Variation and Lung Cancer Risk.

Cancer Research, 52: 6772-6775.

P450IIE1 implicated in nitrosamine carcinogenicity.

Suggest no association w LC risk - but statistically limited.

Monday 5th April. How relevant is it?

EACR XII

Opening ceremony - Ms Laurette Cuttelinx? - Nat Mus of Public Health
v. Anti-smoking.
Replacement of M Michel Lebrun:

Nurnberg Memorial lecture: The Cancer defect in DNA repair deficiency syndromes.

Dirk Bootsma, Dpt of Cell Biology and Genetics, Erasmus University, Rotterdam, the Netherlands.

To be published in full in E.J.C.

XP, CS & Trichothiodystrophy (TTD) = DNA repair deficiency known to be present.

Blooms syndrome etc faircai Anemia Ataxia suspected but not yet known

1st message: Not all DNA repair deficiency syndromes are cancer prone (e.g. XP not CS or TTD)

2nd message: XP = deficiency in Genome overall slow Repair repair & fast acting gene repair

Cockaynes syndrome - deficiency in actual fast excision repair only

Does this mean that it is the overall Genome repair which is important in cancer?

7 patients worldwide with both XP & CS
XP = 7 complementation groups (A-G)
XP-D group are also found in CS & TTD patients
Rodent cell lines which complement human genes
+/- ERCC3 - excision repair genes
ERCC3 cloned corrects defect in XP-B

Position of the mutation on the gene can make large diffs in presentation of disease (XP-B patients 3 - v. diff)

Drosophila 'haywire' = ERCC3 defect in drosophila
what is the essential function?

ERCC3 - found in transcription factor TF-H - ERCC3 found to be essential for unwinding double helix for RNA polase II to transcribe

Science this month Jean-Marc Egly etc ....
Defect in DNA transcription - Thus ERCC3 mutation may prevent optimal expression of genes for growth, mental retardation etc etc
i.e. normal function only when 'optimal' expression present.

Human ERCC6 gene = ? DNA unwinding motifs
ERCC6 may play a role in allowing excision repair to occur at a lesion = shown to be in CS-B

N.B. ERCC-1 = RAD10 + LIVER, liver region (what about RAD3?)
but not found in any human syndromes yet
ERCC-2 = May be XP-D, RAD3 homology
(How does this fit with RAD10, RAD3 complementation?)

Advances also in other groups
Does this mean that ERCC-3 has a non-essential function in transcription but is somehow preferable - if so how is it selected for??

Franco Rilke, N.I. for Study & Cure of Tumors, Milano Italy

Modern Trends in Pathological diagnosis of cancer

Morphological development microinvasion to fully invasive etc can be correlated to genetic events.

David Lane, CCRC Labs, University of Dundee, U.K.)

The p53 Suppressor Gene

Chr 17p; Phosphoprot 393aa; Seq Spec DNA bind; transcription transactivation, oligomerization; G1-S checkpoint control system; Seq mutated in Cancer; Specific binding to viral & ~~human~~ host proteins

p53 - ↓ important protein but KO mice do survive well - cannot be KO mice = knockout mice
essential to normal growth & development.

Accumulation of p53 protein in tumours
Exposure of normal cells to DNA damaging agents ⇒ accumulation of p53 protein - why? = could change gene transcription or a blockage of cell-in

2028541594

or may trigger programmed cell death - apoptosis.
Cell with no functional p53 do not have this response & do not go into apoptosis - but are more susceptible to damage

p53 in syndromes:-
N.B. Head/neck does not bring around accumulation of p53 - seem to need real DNA damage - not just stress.
Factors which stabilise p53
UV, X-rad, MMC, Ethoxide, PUVA ...
Normal physiological response to U.V. light - local accumulation of ~~UV-light~~ p53 - thought to be associated with the induction of a repair pathway.

p53 pathway is a set of gene function - DNA damage → → → p53 → → growth arrest

Defects in p53 itself or in genes upstream or downstream of the p53 pathway will have effects on growth arrest ∴ may be candidates for new tumour suppressor genes in this pathway
e.g. SV40 = downstream (high p53 levels → No growth arrest)

for upstream evidence looked at BS & AT patients - cat'g II Bloom's) found 2 having no p53 accumulation

---

How is p53 regulated might give therapeutic windows?
Function DNA binding affinity of the protein
Series of monoclonal antibodies to specific epitopes in p53 molecule
Adding antibody at C-terminus ↑ DNA binding activity
= negative regulatory domain - phosphorylation site for various kinases
Also interaction with E. coli HSP70 activates DNA binding
(may be linked to damage response)
Oligomerisation site also at C-terminus.

Could therapeutic agents restore p53 function - perhaps.
(pAb421 antibody seems effective) ∴ DNA but sometimes not by ↑ CKII

No evidence of involvement of transcription factors - Jun/Fos etc ...

PARALLEL SYMPOSIUM NO 3 VIRUSES & CANCER

Chairman Harald zur Hausen, Centre for Cancer Research, Heidelberg, Germ.

Co-chairman Allan T van Oosterom, Dpt of Oncology, University Hospital of Antwerp, Belgium.

Invited Speakers [N.B of ~20% cancer burden linked to viruses of ~10% Infection & cancer = widely neglected & ignored could explain alot more than currently aware - also synergy? -]

① Jan I.T. Magrath, NCI Bethesda USA

"The role of Epstein Barr virus in the Pathogenesis of Burkitts Lymphoma"

BL = 50% cancer in children in equatorial Africa. Very climate dependent. Clinical features relate to age & geography. (& endemic level)

4 in immunosuppressed patients

= B cell lymphoid neoplasm - several genetic causes including translocation and mutation of c-myc. Associated w EBV but varies geographically - Mutat of p53 also varies but not geographically (~33%)

Frequent translocation 8-14q32 (80%) } myc/Ig translocation
8-22
8-2

Where & when does Translocation occur? - Recent evidence that very early in pre-B cells

EBV latent genes EBNA-1 - Hypothesis that EBNA 1 contributes to deregulation of c myc

Summary - role of EBV may contribute to the deregulation of c-myc through interaction with EBNA-1 in myc/Ig translocation

---

② P.F. Hofschneider et al. Max Planck Inst, Martinsried FRG.

"Hepatitis B Virus transactivator proteins"

The pkc/AP-1 sig N. path way is likely to rep 1 way of mediating HBx transation

2028541596

PARALLEL SESSION No. MOL. ASPECTS OF CANCER DIAGNOSIS

16:30 onwards:

Human 11q13 associated diseases - Breast cancer, Sq cell cancer etc etc

Identification of functional genes in the 11q13 region:-

B-cell lymphoma location -

① Translocation

What is the responsible gene in this region. PRAD1 / CCND1

= most proximal gene relative to BCL1,

- Lymphomas rearrang in PRAD1 etc etc

② Amplification ⇒ poor prognosis & presence of lymph node metastasis.

Amplified regions harbour 2 potential oncogenes PRAD1 / EMS1 both of which are overexpressed - but there are some amplifications which don't give these genes!! Therefore probably may be other genes involved not yet understood.

Concentrate on EMS1.

EMS 1 = located in adherens junctions at cell-substratum contact sites.

= The chicken homologue, the pp60/c-src protein is a substrate for SRC TK activity

= The chicken protein binds with high affinity to F-actin

= overexpression of EMS-1 in transfectants results in aggregation of

This Reg. interaction of adherence junctions.

overexpression ⇒ disturbance of cell adhesion structures

Since 11q13 amp associated w ↑ invasion - EMS1 might mediate this behaviour.

Conclusion - finding the gene in a known region is very complex so far cannot determine one single gene responsible

2028541597

6th April 1993

Epidemiology: critical assessment of cancer risks with special attention to passive smoking, alcohol intake, asbestos etc. etc

Peter Boyle, (Milan)

MacMahon & Pugh, 1970 = "The scientific study of the distribution & determinants of disease in man"

Increasing attention to epidemiologic findings.

Why: press releases - when sensibly used = good but "planting" premature results = bad & dangerous

& - lay language - cancer stories boost sales - public afraid of cancer

⇒ Change in role of epid

1950-1980 60 - Research, replication

1980 → much more "hit & run" epidemiology

⇒ looking for the "glory" of being the first to show something

Discovering the "important" cause of cancer for the next century

⇒ this changing attitude has lead to recent claims of "causes" of cancer

"Public if asked would say radon & pollen are most important causes & tobacco & smoking would come down the list somewhat" & this is a shame"

Causes of cancer

II Waiters - ↑ git. & lung - poss LC

III Reindeer breeders - Lapps - fallout radiation

IV Height - short < cancer tall ♂ = ↑ breast

V Refrigeration - Refrigerators git etc NY

VI Allergies - ↓ cancer

VII Electric razors - ↑ leukemia (unpublished)

VIII Cellular telephones - No studies due to law case

IX Radar guns - No study urogenital tract cancer in officers

X. Pet Birds - Pigeons 4x etc somewhat noticed

Hidden in list are a number of known & real risks

Unfortunately divert from passive smoking - alcohol

= associated with small but consistent risks

2028541598

Alcohol IARC 1988 - sufficient human evidence, pharynx, larynx, oesophagus & liver for all except liver - multiplicative effect w smoking

Passive smoking - EPA 1993
IARC 1998 - No!!

Asbestos - low dose extrapolations from occupational studies -

EEC 1990 730,000 deaths due to cancer
1,222,000 new cases diagnosed
664,000 ♂ 568,000 ♀
308/100,000 p.a. 214/100,000 p.a.
[Jensen et al 1990 - Eur. J. Cancer 26: 1167-1256]

1990 Breast = 1 Lung = 8 for women

* Trends for future - populations ageing ⇒ 40% No of cases entirely due to ageing
[On what assumptions are these calculations based]
↓ need to plan for this
changes in risk

* Projections re exposure - [what risk factor for lung cancer is increasing? i.e. causing trend]
Why are cervix & stomach ↓ in trend?

Projections from 1990 to 2000 worldwide incidence will ↑ from 6m to >10m
The majority of this is due to ageing
Post war baby boom ⇒ cancer increase boom after year 2000
are important & clear messages obscured by

Last slide on lung cancer trends says generally declining
Central & Eastern Europe - 1/3 deaths in all men is due to tobacco related disease
1985 - 260,000 deaths USSR

Recommend in Europe elimination of cigarette smoking ⇒ 1/2 no of cases ↓ 33.3%
mammography, drugs ⇒ 5 in Europe - Vaccine for HPV ⇒ ↓ 8% worldwide

?'s about Radar; & Chernobyl
Burdeos - "for every purported epidemiological relationship a logical & indeed an illogical explanation & provide a biological plausibility"

2028541599

N.B. claimed clear cohort-birth trend for ↓ of lung cancer in future but in fact recent studies (Netherlands e.g.) suggest that it may not be as simple as we thought.

"No proven that if eliminated smoking today ~~tomorrow~~ and did not replace it with something equally bad or worse, that there would be a reduction of cancer by 1/3 in 30-40 years in Europe"

Parallel Symposium No 4.

MOLECULAR EPIDEMIOLOGY OF CANCER

Chairs: Helmut Bartsch & Marcel Robertfroid

C.P. WILD; Hepatitis B, aflatoxin & hepatocellular cancer (IARC)

Markers - What if there is an inter/individual variability in the affinity for bound makes which may be linked to biological availability in either direction & not related to exposure

Aflatoxin-albumin - relationship maximum found between Plasma albumin & DNA binding in liver (target organ)

Hypothesis:- Combined effect of HBV & Aflat.

GSTM1 genotype associated with level of aflatoxin-albumin levels

No information to suggest that humans detoxify aflatoxin through glutathione conjugation

Cyt P450 2A5

Transgenic HBV mice - expressing Cyt P450 2A5 much more evident & dispersed than normal

Treated w aflatoxin - some suggestion of ↑ adducts in cells with these increased levels

ie viral injection may alter metabolism of aflatoxin but may be many other possible mechanisms

---

Epidemiologic evidence of interaction - relatively weak

P. VINEIS: Molecular Epidemiology of Bladder Cancer
(Turin)

Smoking & Bladder cancer (≈ 50% in western country ↓ 20% ↓)

Black v Black Tobacco

RR for life long users of black = 2-3× higher than Bantu (Italy)

* (Vineis et al Int J Cancer 34, 165 1984) *

Aromatic amines higher in Black than Bantu

4-AB, 2 Naphthylamine

Hb-4-AB adducts - smokers v non-smokers

20a(61) ~~16(20)~~ 31 (25) Italy
~~16(20)~~ 53(28) U.S.

4-AB = bladder carcinogen from epidemiology (occupational exposure)

Genetic susceptibility re - slow acetylators seem to be at a slightly higher risk of bladder cancer probably due to slower inactivation of aromatic amines through acetylation

Some fairly convincing population studies showing that for cases exposed to aromatic amines there are many more non acetylators but non-exposed cases don't!

Relating Hb adducts to acetylation phenotype -

* (Sarkar et al. JNCI 82: 1826 1990) ⇒ Acetylators slow or fast v Hb adducts of Hb in NS, Band & Black - difficult to see trends

P32 DNA adducts :- in exfoliated bladder cells

Slow acetylators ≈ 2× adducts of fast acetylators

Now doing case-control study on bladder cancer - hospitals looking at analyses of DNA adducts for smokers & non smokers assess RR of ? to have these adducts about median levels (so far only with 21 patients) =

In full c/c study will look at acetylation phenotype etc.

ONGOING STUDY

(* Ask Ted about filter technology - anything which could remove the aromatic amines?)

? - could tobacco smoke induce acetylation - No evidence

? Any evidence that slow acetylation could be introduced by presence of a cancer

? Persistance of adducts after cessation - not much data

2028541601

H. Shirima: Chronic infection / inflammation & human cancer: role of nitric oxide (IARC) synthase in carcinogenesis

Smoke	30%	
Chronic infection	≃ 35%	
Unbal diet	≃ 35%	According to B. Ames
Hormone	29%	
Occ	-2	
Pol	-01	
	122%	

(due to multiple causes)

* NO = Mol of year 1992 (Science Dec 11 1992) *

NOS (NO synthase) = NO involved in Vasodilatation, Platelet inhibition, Cell adhesion, Neurotransmission, Penile erection.

Regulation of enzyme & hormone release.

Immune regulation, Cytotoxicity.

Genotoxicity, Nitrosamine formation.

NO released from arginine through NOS - shown by γ interferon & inhibits tumor cells Krebs cycle, DNA synth etc etc.

Very often double edged sword

Nitroxyl radical (NO) ⇒ O_2^- ⇒ $OH^\cdot$ - cellular damage accordingly ?!

NO Genotoxicity: -

NO-releasing compounds:

Hypothesis - Opisthorchis viverrini assoc w. cholangiocarcinoma is mediated by NO

Thailand - Cholangiocarcinoma incidence

* Lancet, 1991; 337: 76-78. - cirrhosis = other NO effects *

* NO in Ulcerative Colitis Lancet 1993 341 465-66 *

D. Forman: A Molecular epidemiological perspective on the etiology of gastric cancer
ICRF, U.K.

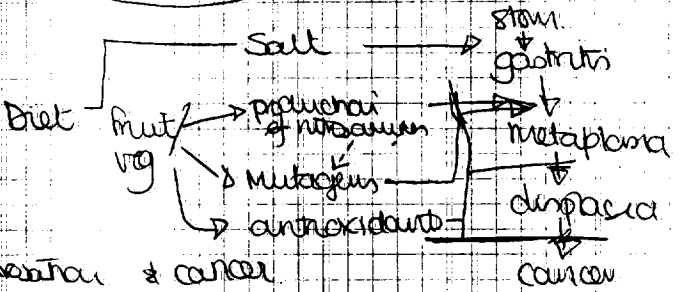
Background: Traditional epidemiology – (Parkin et al 1993 to be published) worldwide distribution of cancer

Gastric cancer virtually universally declining in all countries (except Portugal?)

Dietary factors – fruit/raw veg = favourable (RR 0.4–0.8)
salt = risk factor (RR 1.4–2.0)

Why ↓ – dietary; refrigeration? H. pylori

Model:-



Nitrate nitrosation & cancer

Nitrate unlikely to be rate limiting exposure for gastric cancer

Helicobacter pylori = major cause of gastritis
(Campylobacter?) ⇒ atrophic gastritis ⇒ cancer

H. pylori – appears to reduce available ascorbic acid in gut probably by affecting active transport of vit C into stomach from blood

How can H. pylori be open to intervention as major epidem.

– Because can eradicate can have infected & uninfected individuals quite readily etc etc

DNA adduct assay –; oxidative damage, mutation spectra & mutant index all being looked at.

P. Bruneux dietary fat & breast cancer
(Texas, N)
fatty acid analysis of breast adipose tissue + prognosis
Multivariate analysis of prognostic factors when looked at breakdown of fatty acid type becomes v. strong - largest influence due to
X-linoleic acid (low X-linoleic = marker of uncontainment & metastasis)
Why & how? - would dietary supplementation help?

Dr. Daud. (Portugal)
Only looked at 20 individuals ~~as~~ 31 gastric cancer cases
3 cases showing anti-A staining & A transferase activity
Possible explanation through gene mutation - 'O' phenotype
due to inability to produce A protein - a mutation may
lead to

A. Witschen - predicting cancer risk
(Russia)
Smokers & lung cancer & healthy individuals analysed for
animals in that exhaled higher levels of Diol SP. Non-smokers
healthy than with lung cancer.
Such biomarkers could be useful in predicting human risk

PARALLEL SYMPOSIUM NO 8: ENVIRONMENTAL CARCINOGENESIS: EXPOSURE & MECHS

M. Chorazy - Pollution in Silesia - DNA & chromosomal damage in humans
Poland.
Heavy industry pollution - SO_2, solid waste

Bernadette Schoket - DNA adducts induced by environmental exp.
(NIPH, Hungary)
PAH's & complex mixtures
[No correlation with smokers NS lung cancer & adducts']

Hemminki, K. DNA adducts & genetic changes in exposed humans
Karolinska
foundry workers - 2-3x risk for lung cancer PAH (produced from hot metals
burning the molds
N.B. at work - 2.1 (3 months after vacation) } adduct levels
after vacation 1 (after 4 wks vacation)

2028541604

lymphocyte adducts smokers > NS - (long ½ life)
granulocytes adducts sm = NS (short ½ life)
∴ lymph more sensitive pos because they are around longer
TSN - NNK induced neoplasia & detoxifying drug procarbazine

Between sm & NS - only found stat influence for 7 methylguanine adduct when lymphocytes are analysed
Benedette schoket lung samples from smokers & nonsmokers
dami did find ↑ adducts in bronchi of smokers compared to NS
Also in lung cancer chemotherapy patients
Reasonable corely between bronchial & lymphocyte adducts for 5 ind. only

Styrene
Dreamed molecular epidemiology as a tool to understand the 'black box' between Exposure & disease risk.

M Hollstein, IARC France - p53 mutation in human tumours

Age standardised proportion of regional cancer incidence due to tobacco & alcohol varies from around 90% in Europe but in Xuanwan province in china is only around 1%

Mutational spectrum = pattern of base changes ⇒ location in a defined sequence
p53 gene important because target much larger

4/5 hotspots at CpG sites because Me-C ⇒ T as first mis-repair
What is 'spontaneous' mutation
hotspot 5 is not a CpG site - id. in hepatocarcinoma (249)

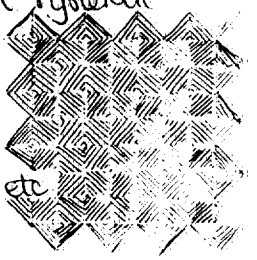
① HCC / AFL & HBV
② skin SC cell cancer & U.V.
③ p53 muts in lung cancer - Most muts - G:C → T:A transversion (≈ 40% comp to breast cancer 28%)
But cannot be absolutely certain of reason for specific spectra as G:C → T:A mutations are not proof of exogenous agents
= Mut in HGPRT seen spontaneous G:C → T:A
Animal cancer tests lagging behind - but animal models may not be very useful because although there is conservation of the amino

acids in the p53 conserved region it is not reflected in the nucleotides - because of the 'flexibility' of the genetic code'.

Other puzzles which might address ⇒ Synergy between tobacco and alcohol - Ashok: are mutation pattern induced by tobacco modulated by alcohol - first guess by comparison of oesophagus & lung but it would be preferable to look for the same site.

M. Dauz: - (Germany).

Communication of disturbance of local growth with systemic system.



R. Pani. Cagliari, Italy - Brest preserve hepatectomy etc

Tariq Tindle. Nitrosation.

Nic in vivo metab mainly under nitrosation NNN, NNK & NNA also bacterially metab to cotinine in tobacco & in human system speculation - nic nitrosated in vivo - spec through in vivo nitrosation of cotinine

NNK = 4# ng/cig. 168 ng/cig NNN

Average smoker estimated exposure - daily exp - 6-93/pg etc

Nasal snuff much higher

IsoNACC identified in urine of 4/120 cigarette smoker - is this endogenously nitrosated nicotine or direct from MS

Volunteers nitrate + cotinine
nitrite + nicotine } acid nitrite

urine collected - No IsoNACC identified in 3 smokers (abstained from smoking)

Conclusion: occasional passive results from exogenous exp
Nitrosation of nicotine to IsoNACC does not occur in experimental conditions

Exposure to NNK ⇒ glucuronide conjugation - 2028541606
ie although exposed seems to be excreted or eliminated
s Health

7th April 93

Walter Birchmeier Inst. Cell Biol. Essen. Germany

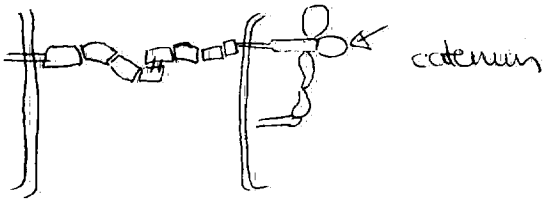
Cell Adhesion molecules and Motility factors in the regulation of tumor cell invasion

E-cadherin necessary to maintain intercellular adhesion in epithelial cells. Also oncogenes

Cadherin - Ca dependent adherent molecules

E-cadherin = epithelial specific cadherin molecule

-Transmembrane



well differentiated carcinomas have almost the same cadherin content as normal but levels go down as the differentiation goes down

What decides if is expressed or not?

E-cadherin promoter - SP1 site; AP1 site; box, E-palindromic sp

found that persons of all 3 regions will work 100% in epithelial but not in fibroblasts & not in poorly differentiated epithelial cells - must be due to transcription factors?

AP-2 like factor probably responsible

Mutations in E-cadherin gene ⇒ dysfunctional molecule

src gene could phosphorylate one of the catenins which could open the gap junctions

Motility factors Scatter factor 90kd. (60kd + 30kd)

Found within hepatocyte growth factors

Gene human chromosome 7 = 1 gene

Receptor = c-MET protooncogene product = transmembrane tyrosine kinase

SF/HGF induces cell motility, tumor cell invasion, morphogenesis growth stimulation and apoptic inhibition

2028541607

Nerve growth factor axis goes through MET

Two types of molecules important in maintaining or destroying the epithelial make-up one is 'recessive' are is 'dominant', Do they play together or are they independent. MET tyrosine kinases may show a significant link.

Adhesion molecules are also signalling molecules
Future work look at activation

PARALLEL SYMPOSIUM No 11

MOLECULAR ASPECTS OF INVASION & METASTASIS

Paul Hart: - Integrins cell-substrate interaction - matrix receptors (U.K.) in malignant melanoma.

Dr C. Cillo, (Naples) Hox genes

183 nucleotide sequence, blood domain
Class I Homeobox containing genes = Hox genes
colinearity of human Hox genes with Drosophila Hox genes

SCLC - 2 histological types -

2028541608

Mary, Mum, HFH: Tom & Dennis, Angela, Tom & Liz, Julian & Ros, John & Liz, Angela & James
[Pete & Denise] [Aunty V.]

Thursday, April 8th 1993

~~① Pass meeting notes to Cory for Typing~~
② Pass requests for references to library
③ Look up Science Dec 18 1992 - Md of the Year NO.—
d. Scientific American 267(6). Dec 1992. p29 & p52
④ Ring Evan Clegg - for Nitch & for Animal Scientific Proc Act. any knowledge?
~~⑤ Copy proceedings of IBEC conference for circulation with meeting notes.~~
~~⑥ Copy Bunny paper & undated for Roger Wall - send to Roger! / Untofo~~
⑦ Write brief notes on bunny undated paper - can draw any conclusions about soybean oil in tumors?
⑧ Spanish presentation - contact Javier Barcia

Monday April 19th 1993.

See above ↗

d ① Bulletin Board Accns.
② Send a list of current references on Atherosclerosis to Unbojo.
③ check LAB refs - have we an original of the 'Harvard' on file.
Do we have the other 2 cited by Harvard & the original Harvard article.... (Refs 11, 12 & 5)
Talk to Helmut about this paper.....

④ Ring Lovesey:- re conference in Munich
⑤ Ring Bob Pages re ① 4-AB paper & our response
~~⑥ Ring Wolf - check arrangements for Wednesday are O.K~~

S.K. Hammond et al. 1993. JNCI 85(6): 474-478. 1993.

"Relationship between Environmental Tobacco smoke exposure and Hemoglobin Adduct levels in Nonsmokers".

This is a report of a continuation of a study on 15 pregnant women where the levels of 4-ABP-Hb adducts are related to reported ETS exposures and compares these to smoking women found in the previous study.

Measurement of ETS exposure through detailed questionnaire, one 7 day diary and a personal monitor. Intensity measure calculated based on No of smokers x No of hours x proximity factor
Air sampling based on nicotine collection
Weekly average nicotine concentration in 3rd trimester used to categorise ETS found good correlation w questionnaire and diary.
N.B ? on exposure to kerosene heaters, gas stoves, fireplaces etc for 4 Nitrobiphenyl contaminants also included
Only 3rd trimester exposure examined. (Change of plan during expt)
N.B for some only 2nd trimester data available :. ~~Need to isolate~~ questionnaire ~~delivery~~ used to ~~Monitor~~ evaluate whether a change had occurred!
(= 12 subjects)
Delivery - Mat & cord blood - 3/12 non smokers = none collected (high ETS)
1/2 smokers in lowest cat. low.

54 preg NS	40 = 4ABP measured	} urine Hb	= 22 pg/g Hb
20 preg S	15 = 4ABP measured		= mean 18 pg/g Hb

4-AB levels will depend on passive smoke exp; smoking & individual Metabolic diffs. (as noted by authors) N.B also exposure to 4-Nitrobiphenyl
Nicotine exposure categorised into low, medium & high ETS exposure groups and calculated mean & median adduct levels in each category.
*4NS had no personal nicotine exposure and were :. excluded. *

N.B surely this is valuable information as gives an idea of "background" exposure female !!?

2028541610

Mean 4-ABP/gHb	Median 4-ABP/gHb (pg)	ETS exp
17.6	15	low
20.8	17	Moderate
27.8	26	High

N.B. refers to other studies - Ref 11 & 12 - should check these out.

"The increase is not dramatic and the public health significance is unclear"
The observation on 4-ABP suggests that the same may be true for potential lung carcinogens e.g. Nitrosamines.

Overview of methods :-

80 smoking women (all 3rd trimester enrolment)

54 non-smoking women

+ 14 non-smoking women recruited later as not all originally were willing in both 2nd & 3rd trimesters.

Compared results from 3rd trimester exposure to 4-ABP adducts at delivery.

Bloods not collected from 3/12 non-smokers in high categ
1/8 " " " low categ.

Unknown interference prevented analysis of blood from 1 NS.

Blood & Hb collected & analysed for 40 NS & 13 S.

Mean levels adducts smokers = 154 pg 4-ABP/gHb
NS 22 pg 4-ABP/gHb

Blood was not collected from 13 NS subjects in this study, 9 through obstetrical emergencies - no explanation for the other 8.

Is 4-Nitrobiphenyl present in tobacco smoke? - If so then fetus may not be exp to the carcinogen 4-ABP but at least in part to 4-NBP.

Left, et al. 1992. (Denmark) Carcinogenesis, vol 13(12): 2241-2247.

Oxidative DNA damage estimated by 8-Hydroxydeoxyguanosine excretion in humans: influence of smoking, gender and body mass index.

300 ♂ + 300 ♀, 40-64 yrs old - Copenhagen

~~398~~ 396 initially participated, 98 ♀ 35 ♂, 11 initially = excluded

diet record, 2 wks; (animal, veg, etc)

tea, coffee, cigarettes & Medicine

Body Mass index.

From bivariate analysis body wt; BMI & smoking were significantly assoc w 8OHdG excretion. Thus 30 smokers had a 30% higher level of 8OHdG than NS.

Dose response not evident.

Multivariate = sex, BMI & smoking

Could be explained by effect on metabolic rate - Health implications unclear.

2028541611

19th April 1993.

A. Penn – Progress report – ETS & atherosclerosis:-

Cockerels:- periaortic fibrosing SS; 2hr/day, 5day/wk, 12 weeks = no effect.
Now look at SS 6hr/d, 5d/wk 16 wks.

Abdominal aorta – 30 SS exp
12 air control
} 6wk → 22 wk scan Rx. 1RYF cigs.

Exposed in 1.3m³ chambers
Plaque Index (Plaque area (mm²)/luminal circumf. (mm) x100)
CO & TSP- daily 3x
Nic weekly.

TSP ≃ 7 - 8 mg/m³.
CO ≃ 39 ppm.
Nic ≃ 380 µg/m³
} N.B = slightly higher than 2nd (low) exposure groups but v. diff comparatively!

primary effect = to make plaques grow faster
Suggest that this could be interpreted as a 'realistic exposure'.

—//—

4-AB story – what response? –

1). St Hammond et al paper shows that 4-AB Hb adducts are detectable in non-smoking women at levels 15-20% of the smoking women.

KRITCHEVSKY, D.

"Dietary Fat and Experimental Atherosclerosis".

Int. J. Tiss. Reac. XIII (2) 59–65. 1991.

Reviews studies relating to the effects of fat unsaturation and fatty acid composition on the development of atherosclerosis in Rabbits:-

Rabbits fed commercial diets as follows.

	Iodine value	Effect on atherosclerosis: serum chol. (mg/dl)	atheroscler. (1–4)
3% chol + 9% saturated fat (shortening)	72	3991	3.71
3% chol + 9% unsat. fat. (corn oil)	130	3150 (↓)	2.71 (↓)
2% corn oil (chol?) + 6% coconut oil	9	2826	3.1
" " " " lard	63	2247 (↓)	2.7 (↓)
" " " " hydrogenated corn oil	79	1984 (↓)	2.5 (↓)
" " " corn oil	124	1907 (↓↓)	1.6. (↓↓)

stearic rich fats.

		serum chol.	atheroscler.	
cocoa butter (35% stearic acid)		1556	1.86	(N.B. should be both coc oil & palm oil - low figures due to bad absorption of ...?)
coconut oil		1649	2.26.	
palm oil		1869	2.19	
corn oil		1064	1.4	

Peanut oil (4-6% long chain sat fatty acids) = atherogenic for rats & monkeys thought due to the long chain behenic & arachidic acids, (Atherosclerosis reduced with PGF = peanut oil minus these fatty acids)

oleic rich fat

corn oil Coton 77B (= 1.05 oleic/linoleic) = ↑ lipidemic, & sudanophilic

corn oil normal. (= 0.43 " " .)

Semipurified cholesterol free diet ⇒ hyperlipoproteinaemia

2028541613

Bob says ring Chris Proctor.!! Tel 00 1 202 662 5908

Dr Mark Rowsell response to the Journal

Dietary sources

Symposium in Tokyo - Monographs. Teruyuki - Nobuhiko

Switzer; Greven. PN Lee. Gilbert.

→ Published Springer Verlag 1993.

Evan Gregg:-

Inbifo 22/08/93

Nicotine in hair -

publication on rat study - melanin important in systemic uptake

- systemic nicotine v. low compared to ETS exp.
- for systemic v. diff to wash out
- ETS easily washed out whether pigmented, non-pigmented etc etc....

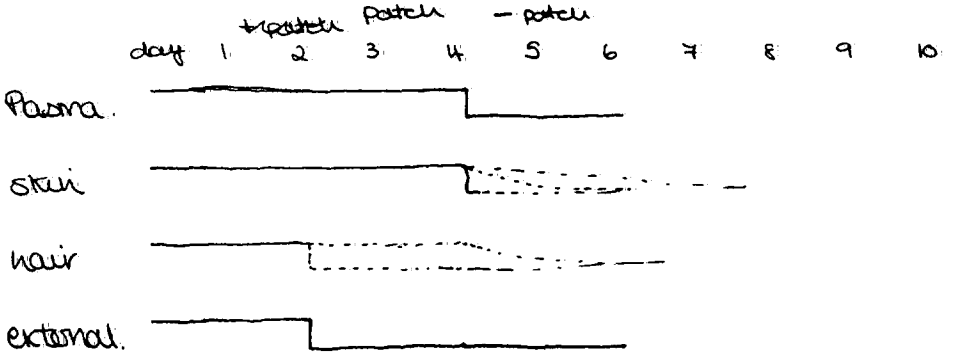
Washing data - should improve before ready for publication - could be done with samples that are left.

Are there differences between internal & external w.r.t. binding.

For external does melanin content make a difference to washability.

- Where to publish. J. Bio of Pharmacology :- (Jim D'Arcans.)
J Drug Metab & Disposition

Why differentiate between systemic & external.? licensing - hospital patch experiment



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Peters list of future concerns:-

1. Effect of crown cycle - (averaged out so probably not important)
2. Effect of washing cycles
3. Effects of bleaching / colour / UV
4. Animal v human hair
5. Vapour phase v ETS (probably being covered in Nilsson?)
6. Rate of cotinine
7. In-vivo production of ~~nicotine~~ cotinine
8. Binding sites nicotine & cotinine
9. Epidemiology - Sm vs NS; HE vs LE ETS. - (Not in bids - but would be "nice")

priority scale:- 2, 3; 7; 8 might be interesting but = totally new story.
Probably no point in further board studies
Cotinine studies using Radioimmunoassay (RIA) highly questionable due to cross-reactivity of the antibody.

6) Can you use cotinine to distinguish between smokers and nonsmokers or between ETS exposure levels. Is there a gradient of ~~nic~~ cotinine along the hair? This could confirm very quickly if there was any external contribution to hair.

2) Will be done by washing procedures. as well included in the 3 studies.

Newborn hair - should we / could we do anything. WRE suggests recalculating concentration. but is it important - probably not.
more direct method - measure plasma level of mother & correlate with nic level in hair.

Summary:- Publish uptake in rats + few data on external uptake & possibly on washout diffs - will evaluate further. try to publish.

- Do not pursue board study but get decline info in Dr Rosner board.
- Treatment study speed up - including cotinine & investigate different pretreatments (some of them as per Peters method
- diffs. bet vapour phase & ETS. exposed

2028541615

22/4/93.

Intro Atherosclerosis morning:

Haverman - Animal studies of note Rogers et al (1988) - baboons.
Penn et al. (1983-1993)

Zhu et al studies Fisher compared to Zhu paper - Zhu says that their results for SS are surprisingly high compared to Fishers MS results - Is this related to increased 'area' of lesions as opposed to increased number? ?

Atheroma - necrotic centre + fibrous cap (humans) - age related
≈ 30-60% people have some sort of lesion.
Theories of atherogenesis = 3 major theories.
Reaction to injury Ross + Glomset. (1976.)
Lipid theory
Monoclonal Theory = benign monoclonal neoplastic growths (1973) Benedict & Benedict.
(has been ?d but are substantial evidence)
Unified theory - reaction to injury & lipid not mutually exclusive
Steinberg (1980).

Animal Models:- N.B. some spontaneous lesions in rabbits.
Requirement ① - Similarity to humans !!
There is no ideal animal model:- depends on what you want to study:-

lipid accumulation	= rabbits
genetics	= pigeon
new drugs	= pigs
relationships/clinical	= primates

Hamsters appear to be more suitable model than rabbits in respect to similarity to human lesions. but measuring areas v. difficult because arteries are so small!! Also may be more suitable for inhalation. but hamster is not widely used - Need to seriously question which is the better model. *

Stress factors: how do we control for this stress.

From Roger Ryander:- Ronald Anderson et al. 1991. Am. Rev. Resp. Dis. 144: 570-574.

Nicotine may be linked to atherogenic profile of HDL/LDL in smokers

CO & Mutagenic smoke components = possibly also relevant.

Possible experimental approaches:-

- determination of lipid hydroperoxides in native LD by chemiluminescence flow injection assay. etc etc....

  determination of platelet aggregation

N.B. Although epidemiology true, mechanisms still not clear.

* Basic background reading of reviews on mechanisms of atherosclerosis - N.B. potential significance of differences between Rabbit & other animals and humans. *

K. Behrens:

2hu repetition study:-

General design of NZW Rabbits, 30/g 3 groups. 1 group / container.

Diet 3.0% Soybean oil } Zeigler Bros.
0.3% cholesterol.

Groups.	Target CO	Conc TPM.
	0	0
Gr 1	20	4
Gr 2	60	20

No intermittent exposure (i.e. no human break as 2hu et al!!)

Biological Assays: Body wt:

Bleeding time: day 1, 6 & 12.

N° of circulating platelet agg.
platelet N°
Hematocrit
Hemoglobin

Lesions:- Determination of area of lesions by morphom.

Aorta & pulm arteries

—//—

Additional coagulation studies should be added.

Sedation of half of each group to take away ~~sedation~~ stress from smoke groups

should we include biochemical determination of cholesterol & cholesteryl esters.

The stress stage is very important - we should also all try and include some way of coping with this. How should these groups be derived - new

2028541617

Sedation groups - postpone until after initial study
P* Any literature on stress induced atherosclerosis. *

Penn paper statistics shows diff SD but not diff of the Mean
Will send complete protocol for first study & probably some proposals for the future on stress

[N.B. 4AB-Hb adducts v. NNK-Hb adducts data doesn't add up ∴ follow up.]

—— // ——

Newrath; ETS dynamics.

* From Tony Tricker - problems with Hbp adducts of NNK ≙ 2-3 x non smokers (in smokers) whereas 4-AB-Hb adducts in the range 5-~~20~~ x ns. why should this be? - Do some background work on ① 4-AB sources

② Hb adducts & their significance

③ What other smoke components have been measured in Hb

④ How does data on DNA 4-AB adducts etc back this up. (see ~~[illegible]~~ Cariolo's paper).

Get 4-AB references to Ted for Monday.

P 28th April 1993.

Telephone call with Bob Pages following our discussions with Inbifo on the Atherosclerosis study

Also - proposal to extrapolate back from human data in E.P.A. to assess what would be expected human incidence in rats.

Also NNK adducts in Hb seem surprisingly high - much higher than we would expect - can we trace this paper / study. (Telephone Tony Tricker)

29th April 1993

Ring Loreen re Scientific affairs directory of ongoing research database

2028541618

30th April 1993.

Reading: -

D. J.W. Van Neck Les Hauts Geneveys:

Molecular aspe Agences immobilières

Béguin, Patrice -

Café - Bois - Soleil 53 50 82 1.

[Natel 077 34 18 56] 22.

Monday May 3rd:

Staff meeting:

S&T organisation: Co.y: IMC with circulation and ordering. → June

Monthly Bibliography to Doreen McAlpin ⇒

SHB ETS news - all scientific papers on stairs ⇒

Reine:- Radar File.

Peter: Projects; Nilsen:

Conrad:

Consultants/contacts. - Schwartz etc

TAC.

May RCA, KH, CE Adelmanetc - IAM to give presentation. RCA Tuesday 11th.

Chuck Wall & others on Wednesday sometimes - no fixed plans.

Meeting next week to discuss project status:

Conrad - a letter

TAC - a letter

Nilsen - nog

PNlee a letter

Last Friday/Monday.

May 14th: morning 9:30 - group meeting

SIT strategy - May 18th 9:00 - 2hrs.

~~Tuesday 25th~~. Tuesday 1st June. 9:30

Friday 14th - Jobdescription

2028541619

Les Hauts Creusets
Agences immobilières
Béguin, Patrick -
Cité - Bois - Soleil
[Natal 077 34 18 56]
53 50 82

20285416 20

30th April 1993.

Reading: -

D. J.W. Van Neck & H.P.J. Bloemers, (1992)

Molecular aspects of pathological processes in the artery wall.
Mol. Biol. Reports. 17: 1-15 1992.

Monday May 3rd:

Staff Meeting:

S&T organisation: Cory: TAC info circulation and ordering. → Jane
Monthly Bibliography to Doreen McAlpin →
SHB ETS news - all scientific papers on stairs →

Elaine:- Radon File.

Peter: Projects; Nilsen:
Conrad:
Consultants/contacts. - Schwartz etc
TAC.

May RCA, KA, CE Advancete - IAM to give presentation. RCA Tuesday 11th.
Chuck Weill & others on Wednesday sometimes - no fixed plans.

Meeting next week to discuss project status:

Conrad - a letter
TAC - a letter
Nilsen - nag
PN Lee a letter

Last Friday/Monday.
May 14th: morning 9:30 - quick meeting
SIT strategy - May 13th 9:00-2hrs
~~Wednesday~~: Tuesday 1st June 9:30

Friday 14th - Jobdescription

2028541621

Banque Populaire Suisse - Boulevard de l'Hopital - juste après M. Nobles 209580 = prenez rendez-vous cardiaque.
[Fr2 - 680,000 -
~~Hersch~~ Herschdorfer - fiduciaire -]
Zuber [27 32 27]

04 Mai 1993

letter from Schmid-Kitsikis. - possibilities but hard for me to see how!

Richard ? [7150 +190] Terminaltray Windows 3.1 - Fax 14 to -

10th May 1993

ETS & Maternal smoking ≙ approx 40 refs.
ETS & children: Physical development (~~ETS & children~~) ≙ approx 30 refs.

Meeting: Projects 1993:

Based on October 14th 1992.
Martinon - dates to be arranged.
- Schmid-Kitsikis for seminar -

Galway - substance use, coping strategies etc etc
Jane Hogan.

SIDS: - review identify consultants ANB - prepare papers for IAM to review.

Next project review meeting. Friday 25th June ~~10:30 - 12:00~~ ~~14:30~~ 14:00h.

2028541622

11/5/93

Check that following refs are included in Passive smoking & Pregnancy review:-

From MSP+1-12:-

Martin & Bracken 1986 "Association of Low Bwt w Passiv. Sm. exp in Preg" Am. J. Ep. 124: 633-642

Rubin et al 1986 "Effect of passive sm on Birth wt. Lancet, ii 415-417

Andresen et al 1982 Cotinine in Amniotic fluid from passive smokers. Lancet i, 791-2

From MSP+1-17:-

Yerushalmy, J. The relationship of parents cig sm. to outcome of pregnancy - implications as to the problem of inferring causation from observed association. Am. J. Epidemiology; 1971 : 93: 443-456.

Ahlborg, G. & Bodin, L. "Tobacco smoke exposure & preg. outcome among working women". Am. J. Epidem. 1991: 133: 338-347

? Smith, N. et al. Tertiary smoking by the fetus; Lancet, 1982 i 1252.

MacMahon et al Infant wt & paternal smoking habits. Am. J. Epidem 1966, 82 247-61

Comstock et Lundin. Parental smoking & perinatal mortal. Am. J. Obst. & Gyn 1967, 29; 1-8

Chen, Y. et al. Passive smoking & low birth wt. Lancet, 1989. ii 54-5.

From MSP+1-22

MacArthur & Knox, Passive smoking and birth weight. Lancet 1984 i : 37-38.

Schwartz-Bickenbach et al. Smoking & passive smoking during pregnancy and early infancy - effects on birthwt etc. Toxicol. Lett. 1984: 35: 73-81.

Trichopoulos, D. Passive smoking, birthweight and estrogens. Lancet, 1986; ii 743.

From MSP+1-26

Mau, G & Netter P. The effects of Paternal smoking on perinatal mortality and the incidence of malformations. Dtsch, Med. Wochenschr. 1974: 99: 1113-18

From MSP+1-40

NRC cites 9 such studies (apparently).

Borlee et al. 1978: Smoking patterns during & before pregnancy: wt, length & head circumference of progeny. Eur. J. Obstet, Gyn & Rep Biol. 1978: 8-171-177

Underwood, et al Parental smoking empirically rel to Preg Outcome. Obstet. Gyn. 1967: 29: 1-8

Rona et al. Exp to cig smoking & childrens growth Int. J. Epid. 1985: 14: 402-9

MSP+1-48

Yerushalmy, J. 1962. in Rosenthal -ctd....

2028541623

From:- Williams, G.M. (1992) "DNA Reactive & epigenetic carcinogens". Exp. Tox. Pathol. 1992: ..., 427-454.

P1KO - ... DNA-reactive carcinogens ... represent human cancer ... not all exposures ... agents lead to cancer -

... = Williams, G.M. et al. "A comparison of the animal & human carcinogenicity of several environmental, occupational and ... chemicals". In. Flamm, ... & Lorentzen, (eds) "... & Toxicity of chemical carcinogens & Mutagens". ... Environmental Toxicology ... Princeton Scientific ..., Princeton NJ. 1985. pp ... - 445.

Also see ... Weisburger ... chemical carcinogens in ... & Doull's ... (p... - ...)

17/05/93.

P's on workplace smoking for H.

4th - Visitors w RIT. Bahrain

Monday 24th Employees managers. - RIT/... HCR.

10th June 3:00; 15th June 10:00 - Trainees.

June 2nd TAC AdHoc group - London. HCR/RDE

Leonard Zahn = chief PR consultant/officer for CTR.

Dr Carol Henry = ...

18/05/93.

Xu etal. Airway Hyperresponsiveness in Cig. smoke exposed Rats. Lung 1993; 171.

From MSPH. - 47

Underwood et al, Parental smoking emp. etc

(Terris & Gold) An epidemiologic study of prematurity, Am. J. Obs & Gyn. 1969; 103 358-370.

(MSPH 49)

(Hood), R.D. - in Ecobichon & Wu. 1990. p241-269.

Brooke O.G., etal. Effects on birt of smoking alc caffeine etc BMJ 1989; 298: 795-801

(Haddow etal), - Am. J. Obst. 1988, 159: 481-4.

(Ahlborg) etal 1989. Pregnancy outcome among working women. Scand. J. Work Environ Hlth. 1989: 15; 227-233.

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